Clinical trial results:
Immunogenicity and Safety of a Tetravalent Dengue Vaccine Administered Concomitantly or Sequentially with Gardasil® in Healthy Subjects Aged 9 to 13 Years in Malaysia

Summary

EudraCT number	2019-003135-36
Trial protocol	Outside EU/EEA
Global end of trial date	27 May 2019

Results information

Result version number	v1 (current)
This version publication date	31 May 2020
First version publication date	31 May 2020

Trial information

Trial identification

Sponsor protocol code	CYD67

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02993757
WHO universal trial number (UTN)	U1111-1161-3376

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur
Sponsor organisation address	14 Espace Henry Vallée, Lyon, France, 69007
Public contact	Trial Transparency Team, Sanofi Pasteur, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi Pasteur, Contact-US@sanofi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 February 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To demonstrate that the humoral immune response (in terms of geometric mean titers [GMTs]) to Gardasil after concomitant administration was non-inferior to sequential administration with the CYD dengue vaccine measured 28 days after the last dose of Gardasil.

- To demonstrate that the humoral immune response to the CYD dengue vaccine after concomitant administration was non-inferior to sequential administration with Gardasil measured 28 days after the last dose of the CYD dengue vaccine.

Protection of trial subjects:

Vaccinations were performed by qualified and trained study personnel. Subjects with allergy to any of the vaccine components were not vaccinated. After vaccination, subjects were also kept under clinical observation for 30 minutes to ensure their safety. Appropriate medical equipment were also available on site in case of any immediate allergic reactions.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Malaysia: 528
Worldwide total number of subjects	528
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	422
Adolescents (12-17 years)	106

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study subjects were enrolled from 01 December 2016 to 16 April 2017 at 5 centres in Malaysia. A total of 528 subjects were enrolled and randomised in this study.

Pre-assignment

Screening details:

As per protocol amendment 1, only dengue immune subjects at baseline completed the dengue vaccination schedule and received 3 doses of CYD dengue vaccine, whereas most of the dengue non-immune subjects received only 2 doses of CYD dengue vaccine. All subjects were followed for safety up to 6 months after the last vaccination.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	CYD Dengue Vaccine + Gardasil (Concomitant Administration)

Arm description:

Dengue immune subjects (i.e., titers greater than or equal to (>=)10 (1/dilution [dil]) for at least one serotype with the parental dengue virus strains in the baseline sample) received 3 doses of CYD dengue vaccine 0.5 millilitre (mL) subcutaneously (SC) at Day 0, Month 6, and Month 12; whereas dengue non-immune subjects (i.e., titers <10 (1/dil) for all serotypes with parental dengue virus strains with available and "valid" results in the baseline sample) received only 2 doses of CYD vaccine at Day 0 and Month 6. Both immune and non-immune subjects received 2 doses of Gardasil vaccine 0.5 mL Intramuscular (IM), concomitantly with the first 2 doses of CYD dengue vaccine.

Arm type	Experimental
Investigational medicinal product name	CYD Dengue Vaccine
Investigational medicinal product code	
Other name	Dengvaxia
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL, SC injection at Day 0, Month 6, and Month 12, respectively.

Investigational medicinal product name	Gardasil vaccine (recombinant quadrivalent Human Papillomavirus (HPV) [types 6, 11, 16, 18] vaccine)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, IM injection at Day 0 and Month 6, respectively.

Arm title	CYD Dengue Vaccine + Gardasil (Sequential Administration)

Arm description:

Dengue immune subjects i.e., subjects with titers >=10 (1/dil) for at least one serotype with the parental dengue virus strains in the baseline sample) received 3 doses of CYD dengue vaccine 0.5 mL SC at Month 1, Month 7, and Month 13; whereas dengue non-immune subjects (i.e., subjects with titers <10 (1/dil) for all serotypes with parental dengue virus strains with available and "valid" results in the baseline sample) received only 2 doses of CYD vaccine at Month 1 and Month 7. Both immune and non-immune subjects received 2 doses of Gardasil vaccine 0.5 mL IM at Day 0 and Month 6 sequentially (i.e., one month before) to each of the first 2 doses of CYD dengue vaccine.

Arm type	Experimental
Investigational medicinal product name	CYD Dengue Vaccine
Investigational medicinal product code	
Other name	Dengvaxia
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL, SC injection at Months 1, 7, and 13, respectively.

Investigational medicinal product name	Gardasil vaccine (recombinant quadrivalent HPV [types 6, 11, 16, 18] vaccine)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, IM injection at Day 0 and Month 6, respectively.

Number of subjects in period 1	CYD Dengue Vaccine + Gardasil (Concomitant Administration)	CYD Dengue Vaccine + Gardasil (Sequential Administration)
Started	266	262
Safety Analysis Set (SafAS)	263	260
Completed	102	84
Not completed	164	178
Non compliance with the protocol	155	170
Lost to follow-up	1	-
Voluntary withdrawal not due to an adverse event	8	8

Baseline characteristics

Reporting groups	
Reporting group title	CYD Dengue Vaccine + Gardasil (Concomitant Administration)
Reporting group description:	
Dengue immune subjects (i.e., titers greater than or equal to (>=)10 (1/dilution [dil]) for at least one serotype with the parental dengue virus strains in the baseline sample) received 3 doses of CYD dengue vaccine 0.5 millilitre (mL) subcutaneously (SC) at Day 0, Month 6, and Month 12; whereas dengue non-immune subjects (i.e., titers <10 (1/dil) for all serotypes with parental dengue virus strains with available and "valid" results in the baseline sample) received only 2 doses of CYD vaccine at Day 0 and Month 6. Both immune and non-immune subjects received 2 doses of Gardasil vaccine 0.5 mL Intramuscular (IM), concomitantly with the first 2 doses of CYD dengue vaccine.	
Reporting group title	CYD Dengue Vaccine + Gardasil (Sequential Administration)
Reporting group description:	
Dengue immune subjects i.e., subjects with titers >=10 (1/dil) for at least one serotype with the parental dengue virus strains in the baseline sample) received 3 doses of CYD dengue vaccine 0.5 mL SC at Month 1, Month 7, and Month 13; whereas dengue non-immune subjects (i.e., subjects with titers <10 (1/dil) for all serotypes with parental dengue virus strains with available and "valid" results in the baseline sample) received only 2 doses of CYD vaccine at Month 1 and Month 7. Both immune and non-immune subjects received 2 doses of Gardasil vaccine 0.5 mL IM at Day 0 and Month 6 sequentially (i.e., one month before) to each of the first 2 doses of CYD dengue vaccine.	

Reporting group values	CYD Dengue Vaccine + Gardasil (Concomitant Administration)	CYD Dengue Vaccine + Gardasil (Sequential Administration)	Total
Number of subjects	266	262	528
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	10.4	10.5	
standard deviation	± 1.20	± 1.18	-
Gender categorical			
Units: Subjects			
Female	175	172	347
Male	91	90	181
Dengue Seropositivity Status			
Dengue immune subjects were defined as subjects with titers >=10 (1/dil) for at least one serotype with the parental dengue virus strains in the baseline sample. Dengue non-immune subjects were defined as subjects with titers <10 (1/dil) for all serotypes with parental dengue virus strains with available and “valid” results in the baseline sample.			
Units: Subjects			
Dengue immune	109	88	197
Dengue non-immune	157	174	331

End points

End points reporting groups

Reporting group title	CYD Dengue Vaccine + Gardasil (Concomitant Administration)

Reporting group description:

Dengue immune subjects (i.e., titers greater than or equal to (>=)10 (1/dilution [dil]) for at least one serotype with the parental dengue virus strains in the baseline sample) received 3 doses of CYD dengue vaccine 0.5 millilitre (mL) subcutaneously (SC) at Day 0, Month 6, and Month 12; whereas dengue non-immune subjects (i.e., titers <10 (1/dil) for all serotypes with parental dengue virus strains with available and "valid" results in the baseline sample) received only 2 doses of CYD vaccine at Day 0 and Month 6. Both immune and non-immune subjects received 2 doses of Gardasil vaccine 0.5 mL Intramuscular (IM), concomitantly with the first 2 doses of CYD dengue vaccine.

Reporting group title	CYD Dengue Vaccine + Gardasil (Sequential Administration)

Reporting group description:

Dengue immune subjects i.e., subjects with titers >=10 (1/dil) for at least one serotype with the parental dengue virus strains in the baseline sample) received 3 doses of CYD dengue vaccine 0.5 mL SC at Month 1, Month 7, and Month 13; whereas dengue non-immune subjects (i.e., subjects with titers <10 (1/dil) for all serotypes with parental dengue virus strains with available and "valid" results in the baseline sample) received only 2 doses of CYD vaccine at Month 1 and Month 7. Both immune and non-immune subjects received 2 doses of Gardasil vaccine 0.5 mL IM at Day 0 and Month 6 sequentially (i.e., one month before) to each of the first 2 doses of CYD dengue vaccine.

Primary: Geometric Mean Titers (GMTs) Against Each Gardasil Vaccine HPV Antigen (HPV-6, HPV-11, HPV-16, HPV-18) 28 Days After Last Gardasil Vaccination in the Previously Dengue Immune Subjects

End point title	Geometric Mean Titers (GMTs) Against Each Gardasil Vaccine HPV Antigen (HPV-6, HPV-11, HPV-16, HPV-18) 28 Days After Last Gardasil Vaccination in the Previously Dengue Immune Subjects

End point description:

GMTs (measured in milli-Merck Units per mL [mMU/mL]) against each Gardasil HPV antigen (HPV-6, HPV-11, HPV-16, HPV-18) was assessed using competitive Luminex immunoassay (cLIA) method. Dengue immune subjects at Baseline were defined as subjects with titers >=10 (1/dil) for at least one serotype with the parental dengue virus strains. Analysis was performed on full analysis set (FAS) which included subset of subjects who received at least one dose of each of the study vaccines (CYD and Gardasil), analysed by baseline dengue status and vaccine group randomized. Here, 'number of subjects analysed' = subjects evaluable and had available data for this endpoint.

End point type	Primary

End point timeframe:

28 days after the last Gardasil vaccination

End point values	CYD Dengue Vaccine + Gardasil (Concomitant Administration)	CYD Dengue Vaccine + Gardasil (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	86		
Units: mMU/mL				
geometric mean (confidence interval 95%)				
HPV-6	420 (327 to 539)	428 (314 to 583)		

HPV-11	1288 (1089 to 1522)	1601 (1323 to 1937)		
HPV-16	6221 (5093 to 7598)	7629 (6142 to 9475)		
HPV-18	829 (682 to 1007)	1042 (858 to 1266)		

Statistical analyses

Statistical analysis title	Antigen HPV-6
Comparison groups	CYD Dengue Vaccine + Gardasil (Concomitant Administration) v CYD Dengue Vaccine + Gardasil (Sequential Administration)
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	GMT ratio
Point estimate	0.982
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.664
upper limit	1.45

Statistical analysis title	Antigen HPV-11
Comparison groups	CYD Dengue Vaccine + Gardasil (Concomitant Administration) v CYD Dengue Vaccine + Gardasil (Sequential Administration)
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	GMT ratio
Point estimate	0.804
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.626
upper limit	1.03

Statistical analysis title	Antigen HPV-16
Comparison groups	CYD Dengue Vaccine + Gardasil (Concomitant Administration) v CYD Dengue Vaccine + Gardasil (Sequential Administration)

Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	GMT ratio
Point estimate	0.815
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.608
upper limit	1.09

Statistical analysis title	Antigen HPV-18
Comparison groups	CYD Dengue Vaccine + Gardasil (Concomitant Administration) v CYD Dengue Vaccine + Gardasil (Sequential Administration)
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	GMT ratio
Point estimate	0.795
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.603
upper limit	1.05

Primary: Geometric Mean Titers Against Each Parental Dengue Virus Serotype 28 Days After Third CYD Dengue Vaccination in the Previously Dengue Immune Subjects

End point title	Geometric Mean Titers Against Each Parental Dengue Virus Serotype 28 Days After Third CYD Dengue Vaccination in the Previously Dengue Immune Subjects

End point description:

The GMTs against each of the four parental dengue virus serotypes (1, 2, 3 and 4) of CYD dengue vaccine was assessed using the 50 percent (%) plaque reduction neutralization test (PRNT50) assay. Dengue immune subjects at Baseline were defined as subjects with titers >=10 (1/dil) for at least one serotype with the parental dengue virus strains. Analysis was performed on FAS population. Here, 'number of subjects analysed'=subjects evaluable and had available data for this endpoint.

End point type	Primary

End point timeframe:

28 days after third CYD dengue vaccination

End point values	CYD Dengue Vaccine + Gardasil (Concomitant Administration)	CYD Dengue Vaccine + Gardasil (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	84		
Units: titer (1/dilution)				
geometric mean (confidence interval 95%)				
Serotype 1	447 (303 to 659)	453 (313 to 656)		
Serotype 2	561 (408 to 771)	717 (526 to 977)		
Serotype 3	460 (354 to 596)	549 (411 to 734)		
Serotype 4	323 (263 to 398)	303 (255 to 359)		

Statistical analyses

Statistical analysis title	Serotype 1
Comparison groups	CYD Dengue Vaccine + Gardasil (Concomitant Administration) v CYD Dengue Vaccine + Gardasil (Sequential Administration)
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	GMT ratio
Point estimate	0.987
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.574
upper limit	1.7

Statistical analysis title	Serotype 2
Comparison groups	CYD Dengue Vaccine + Gardasil (Concomitant Administration) v CYD Dengue Vaccine + Gardasil (Sequential Administration)
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	GMT ratio
Point estimate	0.783
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.22

Statistical analysis title	Serotype 3
Comparison groups	CYD Dengue Vaccine + Gardasil (Concomitant Administration) v CYD Dengue Vaccine + Gardasil (Sequential Administration)
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	GMT ratio
Point estimate	0.836
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.568
upper limit	1.23

Statistical analysis title	Serotype 4
Comparison groups	CYD Dengue Vaccine + Gardasil (Concomitant Administration) v CYD Dengue Vaccine + Gardasil (Sequential Administration)
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	GMT ratio
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.813
upper limit	1.4

Secondary: Percentage of Subjects With Seroconversion Against Each Gardasil HPV Antigen (HPV-6, HPV-11, HPV-16, HPV-18) 28 Days After Last Dose of Gardasil in the Previously Dengue Immune Subjects

End point title	Percentage of Subjects With Seroconversion Against Each Gardasil HPV Antigen (HPV-6, HPV-11, HPV-16, HPV-18) 28 Days After Last Dose of Gardasil in the Previously Dengue Immune Subjects

End point description:

Neutralising antibodies against each Gardasil HPV antigen (HPV-6, HPV-11, HPV-16, HPV-18) was assessed using cLIA method. Seroconversion was defined as changing serostatus from seronegative at Baseline to seropositive (subjects with a pre-vaccination titer < lower limit of quantification [LLOQ] (mMU/mL) to a post-vaccination titer >= LLOQ) or >=4-fold rise in antibody titer if seropositive at baseline. The LLOQ for HPV-6 and HPV-16 was 11 mMU/mL, 8 mMU/mL for HPV-11, and 10 mMU/mL for HPV-18. Dengue immune subjects at Baseline were defined as subjects with titers >=10 (1/dil) for at least one serotype with the parental dengue virus strains. Analysis was performed on FAS population. Here, 'number of subjects analysed'=subjects evaluable and had available data for this endpoint.

End point type	Secondary

End point timeframe:

28 days after the last Gardasil vaccination

End point values	CYD Dengue Vaccine + Gardasil (Concomitant Administration)	CYD Dengue Vaccine + Gardasil (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	81		
Units: percentage of subjects				
number (confidence interval 95%)				
HPV-6	98.1 (93.2 to 99.8)	100.0 (95.5 to 100.0)		
HPV-11	100.0 (96.5 to 100.0)	100.0 (95.5 to 100.0)		
HPV-16	100.0 (96.5 to 100.0)	100.0 (95.5 to 100.0)		
HPV-18	100.0 (96.5 to 100.0)	100.0 (95.5 to 100.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers Against Each Gardasil HPV Antigen (HPV-6, HPV-11, HPV-16, HPV-18) at Day 0 and 28 Days After Each Dose of Gardasil in the Previously Dengue Immune Subjects

End point title	Geometric Mean Titers Against Each Gardasil HPV Antigen (HPV-6, HPV-11, HPV-16, HPV-18) at Day 0 and 28 Days After Each Dose of Gardasil in the Previously Dengue Immune Subjects

End point description:

The GMTs (measured in mMU/mL) against each Gardasil HPV antigen (HPV-6, HPV-11, HPV-16, HPV-18) was assessed using cLIA method. Dengue immune subjects at Baseline were defined as subjects with titers >=10 (1/dil) for at least one serotype with the parental dengue virus strains. Analysis was performed on FAS. Here, 'number of subjects analysed'=subjects evaluable and had available data for this endpoint and ‘n’=subjects with available data for each specified categories and '99999' signifies that the 95% confidence interval was not computable, since all subjects had the same value.

End point type	Secondary

End point timeframe:

Day 0 (pre-vaccination) and 28 days after Gardasil vaccination 1 and 2

End point values	CYD Dengue Vaccine + Gardasil (Concomitant Administration)	CYD Dengue Vaccine + Gardasil (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	88		
Units: mMU/mL				
geometric mean (confidence interval 95%)				
HPV-6: Day 0 (n=108,82)	5.70 (5.46 to 5.95)	5.61 (5.46 to 5.77)		
HPV-6: 28 days post vaccination 1 (n=107,88)	54.9 (45.0 to 66.9)	61.8 (49.7 to 76.9)		
HPV-6: 28 days post vaccination 2 (n=104,86)	420 (327 to 539)	428 (314 to 583)		
HPV-11: Day 0 (n=108,82)	4.16 (3.92 to 4.41)	4.00 (-99999 to 99999)		
HPV-11: 28 days post vaccination 1 (n=107,88)	58.1 (47.6 to 71.0)	78.5 (62.5 to 98.6)		
HPV-11: 28 days post vaccination 2 (n=104,86)	1288 (1089 to 1522)	1601 (1323 to 1937)		
HPV-16: Day 0 (n=108,82)	5.62 (5.38 to 5.87)	5.50 (-99999 to 99999)		
HPV-16: 28 days post vaccination 1 (n=107,88)	148 (119 to 185)	150 (116 to 193)		
HPV-16: 28 days post vaccination 2 (n=104,86)	6221 (5093 to 7598)	7629 (6142 to 9475)		
HPV-18: Day 0 (n=108,82)	5.26 (5.03 to 5.50)	5.06 (4.94 to 5.18)		
HPV-18: 28 days post vaccination 1 (n=107,88)	23.5 (18.7 to 29.4)	31.6 (24.9 to 40.0)		
HPV-18: 28 days post vaccination 2 (n=104,86)	829 (682 to 1007)	1042 (858 to 1266)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers Against Each Dengue Virus Serotype of CYD Dengue Vaccine at Day 0 and 28 Days After Each Dose of CYD Dengue Vaccination in the Previously Dengue Immune Subjects

End point title	Geometric Mean Titers Against Each Dengue Virus Serotype of CYD Dengue Vaccine at Day 0 and 28 Days After Each Dose of CYD Dengue Vaccination in the Previously Dengue Immune Subjects

End point description:

The GMTs against each of the four parental dengue virus serotypes (1, 2, 3, and 4) of CYD dengue vaccine was assessed using the PRNT50 assay. Dengue immune subjects at Baseline were defined as subjects with titers >=10 (1/dil) for at least one serotype with the parental dengue virus strains. Analysis was performed on FAS. Here, 'number of subjects analysed'=subjects evaluable and had available data for this endpoint and ‘n’=subjects with available data for each specified categories.

End point type	Secondary

End point timeframe:

Day 0 (pre-vaccination) and 28 days after each CYD dengue vaccination

End point values	CYD Dengue Vaccine + Gardasil (Concomitant Administration)	CYD Dengue Vaccine + Gardasil (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	88		
Units: titer (1/dilution)				
geometric mean (confidence interval 95%)				
Serotype 1: Day 0 (n=109,88)	62.3 (40.7 to 95.5)	81.5 (49.4 to 135)		
Serotype 1: 28 days post vaccination 1 (n=107,88)	382 (245 to 597)	449 (268 to 752)		
Serotype 1: 28 days post vaccination 2 (n=104,87)	403 (270 to 602)	529 (342 to 819)		
Serotype 1: 28 days post vaccination 3 (n=102,84)	447 (303 to 659)	453 (313 to 656)		
Serotype 2: Day 0 (n=109,88)	110 (75.5 to 160)	130 (84.0 to 201)		
Serotype 2: 28 days post vaccination 1 (n=107,88)	750 (500 to 1124)	848 (541 to 1330)		
Serotype 2: 28 days post vaccination 2 (n=104,87)	728 (519 to 1019)	937 (654 to 1342)		
Serotype 2: 28 days post vaccination 3 (n=102,84)	561 (408 to 771)	717 (526 to 977)		
Serotype 3: Day 0 (n=109,87)	72.3 (52.7 to 99.2)	96.7 (64.9 to 144)		
Serotype 3: 28 days post vaccination 1 (n=106,88)	432 (304 to 614)	517 (355 to 755)		
Serotype 3: 28 days post vaccination 2 (n=104,87)	389 (299 to 506)	543 (403 to 731)		
Serotype 3: 28 days post vaccination 3 (n=102,84)	460 (354 to 596)	549 (411 to 734)		
Serotype 4: Day 0 (n=109,88)	26.3 (18.8 to 36.7)	23.7 (16.2 to 34.8)		
Serotype 4: 28 days post vaccination 1 (n=107,88)	330 (234 to 464)	286 (204 to 401)		
Serotype 4: 28 days post vaccination 2 (n=104,87)	284 (229 to 352)	282 (225 to 353)		
Serotype 4: 28 days post vaccination 3 (n=102,83)	323 (263 to 398)	303 (255 to 359)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Neutralising Antibody Titers Against Each of the 4 Dengue Virus Serotypes of CYD Dengue Vaccine at Day 0 And 28 Days After Each Dose of CYD Dengue Vaccination in the Previously Dengue Immune Subjects

End point title	Percentage of Subjects With Neutralising Antibody Titers Against Each of the 4 Dengue Virus Serotypes of CYD Dengue Vaccine at Day 0 And 28 Days After Each Dose of CYD Dengue

	Vaccination in the Previously Dengue Immune Subjects

End point description:

Dengue neutralising antibody levels against each of the 4 dengue virus serotypes (1, 2, 3, and 4) was measured by PRNT50. Dengue immune subjects at Baseline were defined as subjects with titers >=10 (1/dil) for at least one serotype with the parental dengue virus strains. Analysis was performed on FAS. Here, 'number of subjects analysed'=subjects evaluable and had available data for this endpoint and 'n'=subjects with available data for each specified categories.

End point type	Secondary

End point timeframe:

Day 0 (pre-vaccination) and 28 days after each CYD dengue vaccination

End point values	CYD Dengue Vaccine + Gardasil (Concomitant Administration)	CYD Dengue Vaccine + Gardasil (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	88		
Units: percentage of subjects				
number (confidence interval 95%)				
Serotype 1: Day 0 (n=109,88)	66.1 (56.4 to 74.9)	72.7 (62.2 to 81.7)		
Serotype 1: 28 days post vaccination 1 (n=107,88)	91.6 (84.6 to 96.1)	90.9 (82.9 to 96.0)		
Serotype 1: 28 days post vaccination 2 (n=104,87)	96.2 (90.4 to 98.9)	95.4 (88.6 to 98.7)		
Serotype 1: 28 days post vaccination 3 (n=102,84)	95.1 (88.9 to 98.4)	100.0 (95.7 to 100.0)		
Serotype 2: Day 0 (n=109,88)	83.5 (75.2 to 89.9)	81.8 (72.2 to 89.2)		
Serotype 2: 28 days post vaccination 1 (n=107,88)	93.5 (87.0 to 97.3)	92.0 (84.3 to 96.7)		
Serotype 2: 28 days post vaccination 2 (n=104,87)	99.0 (94.8 to 100.0)	97.7 (91.9 to 99.7)		
Serotype 2: 28 days post vaccination 3 (n=102,84)	97.1 (91.6 to 99.4)	98.8 (93.5 to 100.0)		
Serotype 3: Day 0 (n=109,87)	89.0 (81.6 to 94.2)	86.2 (77.1 to 92.7)		
Serotype 3: 28 days post vaccination 1 (n=106,88)	96.2 (90.6 to 99.0)	97.7 (92.0 to 99.7)		
Serotype 3: 28 days post vaccination 2 (n=104,87)	100.0 (96.5 to 100.0)	100.0 (95.8 to 100.0)		
Serotype 3: 28 days post vaccination 3 (n=102,84)	99.0 (94.7 to 100.0)	100.0 (95.7 to 100.0)		
Serotype 4: Day 0 (n=109,88)	59.6 (49.8 to 68.9)	54.5 (43.6 to 65.2)		
Serotype 4: 28 days post vaccination 1 (n=107,88)	93.5 (87.0 to 97.3)	98.9 (93.8 to 100.0)		
Serotype 4: 28 days post vaccination 2 (n=104,87)	100.0 (96.5 to 100.0)	100.0 (95.8 to 100.0)		
Serotype 4: 28 days post vaccination 3 (n=102,84)	100.0 (96.4 to 100.0)	100.0 (95.7 to 100.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Neutralising Antibody Titers Above Pre-defined Thresholds Against at Least 1,2,3,or4 Serotypes of CYD Dengue Vaccine at Day 0 And 28 Days After Each Dose of CYD Dengue Vaccination in the Previously Dengue Immune Subjects

End point title	Percentage of Subjects With Neutralising Antibody Titers Above Pre-defined Thresholds Against at Least 1,2,3,or4 Serotypes of CYD Dengue Vaccine at Day 0 And 28 Days After Each Dose of CYD Dengue Vaccination in the Previously Dengue Immune Subjects

End point description:

Dengue neutralising antibody levels against each of the 4 dengue virus serotypes (1, 2, 3, and 4) were measured by PRNT50. Dengue immune subjects at Baseline were defined as subjects with titers >=10 (1/dil) for at least one serotype with the parental dengue virus strains. Percentage of subjects with neutralizing antibody titers above pre-defined thresholds (>=10 and >=100 [1/dil]) against at least 1, 2, 3, or 4 serotypes of CYD dengue vaccine were reported. Analysis was performed on FAS. Here, 'number of subjects analysed'=subjects evaluable and had available data for this endpoint and ‘n’=subjects with available data for each specified categories. Here "vac"=vaccination in the specified categories.

End point type	Secondary

End point timeframe:

Day 0 (pre-vaccination) and 28 days after each CYD dengue vaccination

End point values	CYD Dengue Vaccine + Gardasil (Concomitant Administration)	CYD Dengue Vaccine + Gardasil (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	88		
Units: percentage of subjects				
number (confidence interval 95%)				
At least 1 Serotype:Day 0:>=10(1/dil)(n=109,88)	100.0 (96.7 to 100.0)	100.0 (95.9 to 100.0)		
At least 1 Serotype:Day 0:>=100(1/dil)(n=109,88)	90.8 (83.8 to 95.5)	88.6 (80.1 to 94.4)		
At least1 Serotype:post-vac1:>=10(1/dil)(n=107,88)	97.2 (92.0 to 99.4)	100.0 (95.9 to 100.0)		
At least1Serotype:post-vac1:>=100(1/dil)(n=107,88)	95.3 (89.4 to 98.5)	96.6 (90.4 to 99.3)		
At least1 Serotype:post-vac2:>=10(1/dil)(n=104,87)	100.0 (96.5 to 100.0)	100.0 (95.8 to 100.0)		
At least1Serotype:post-vac2:>=100(1/dil)(n=104,87)	96.2 (90.4 to 98.9)	98.9 (93.8 to 100.0)		
At least1 Serotype:post-vac3:>=10(1/dil)(n=102,84)	100.0 (96.4 to 100.0)	100.0 (95.7 to 100.0)		
At least1Serotype:post-vac3:>=100(1/dil)(n=102,84)	98.0 (93.1 to 99.8)	97.6 (91.7 to 99.7)		
At least 2 Serotype:Day 0:>=10(1/dil)(n=109,88)	84.4 (76.2 to 90.6)	81.8 (72.2 to 89.2)		
At least 2 Serotype:Day 0:>=100(1/dil)(n=109,88)	34.9 (26.0 to 44.6)	39.8 (29.5 to 50.8)		
At least2 Serotype:post-vac1:>=10(1/dil)(n=107,88)	94.4 (88.2 to 97.9)	97.7 (92.0 to 99.7)		

At least2Serotype:post-vac1:>=100(1/dil)(n=107,88)	85.0 (76.9 to 91.2)	80.7 (70.9 to 88.3)		
At least2 Serotype:post-vac2:>=10(1/dil)(n=104,87)	100.0 (96.5 to 100.0)	100.0 (95.8 to 100.0)		
At least2Serotype:post-vac2:>=100(1/dil)(n=104,87)	84.6 (76.2 to 90.9)	92.0 (84.1 to 96.7)		
At least2 Serotype:post-vac3:>=10(1/dil)(n=102,84)	100.0 (96.4 to 100.0)	100.0 (95.7 to 100.0)		
At least2Serotype:post-vac3:>=100(1/dil)(n=102,84)	93.1 (86.4 to 97.2)	94.0 (86.7 to 98.0)		
At least 3 Serotype:Day 0:>=10(1/dil)(n=109,88)	71.6 (62.1 to 79.8)	69.3 (58.6 to 78.7)		
At least 3 Serotype:Day 0:>=100(1/dil)(n=109,88)	23.9 (16.2 to 33.0)	27.3 (18.3 to 37.8)		
At least3 Serotype:post-vac1:>=10(1/dil)(n=107,88)	92.5 (85.8 to 96.7)	92.0 (84.3 to 96.7)		
At least3Serotype:post-vac1:>=100(1/dil)(n=107,88)	75.7 (66.5 to 83.5)	73.9 (63.4 to 82.7)		
At least3 Serotype:post-vac2:>=10(1/dil)(n=104,87)	99.0 (94.8 to 100.0)	98.9 (93.8 to 100.0)		
At least3Serotype:post-vac2:>=100(1/dil)(n=104,87)	77.9 (68.7 to 85.4)	86.2 (77.1 to 92.7)		
At least3 Serotype:post-vac3:>=10(1/dil)(n=102,84)	97.1 (91.6 to 99.4)	100.0 (95.7 to 100.0)		
At least3Serotype:post-vac3:>=100(1/dil)(n=102,84)	83.3 (74.7 to 90.0)	88.1 (79.2 to 94.1)		
At least 4 Serotype:Day 0:>=10(1/dil)(n=109,87)	42.2 (32.8 to 52.0)	43.7 (33.1 to 54.7)		
At least 4 Serotype:Day 0:>=100(1/dil)(n=109,87)	6.4 (2.6 to 12.8)	12.6 (6.5 to 21.5)		
At least4 Serotype:post-vac1:>=10(1/dil)(n=106,88)	90.6 (83.3 to 95.4)	89.8 (81.5 to 95.2)		
At least4Serotype:post-vac1:>=100(1/dil)(n=106,88)	60.4 (50.4 to 69.7)	62.5 (51.5 to 72.6)		
At least4 Serotype:post-vac2:>=10(1/dil)(n=104,87)	96.2 (90.4 to 98.9)	94.3 (87.1 to 98.1)		
At least4Serotype:post-vac2:>=100(1/dil)(n=104,87)	67.3 (57.4 to 76.2)	75.9 (65.5 to 84.4)		
At least4 Serotype:post-vac3:>=10(1/dil)(n=102,84)	94.1 (87.6 to 97.8)	98.8 (93.5 to 100.0)		
At least4Serotype:post-vac3:>=100(1/dil)(n=102,84)	72.5 (62.8 to 80.9)	77.4 (67.0 to 85.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Immediate Adverse Events (AEs) Following Vaccination With Gardasil or CYD Dengue Vaccine

End point title	Number of Subjects Reporting Immediate Adverse Events (AEs) Following Vaccination With Gardasil or CYD Dengue Vaccine

End point description:

Any unsolicited systemic AE occurred during the first 30 minutes post-vaccination was recorded on the case report form (CRF) as immediate AE. At Visit 1 and Visit 4, subjects from Group 1 received both Gardasil and CYD vaccination and subjects from Group 2 received only Gardasil vaccination. At Visit 2 and Visit 5, only subjects from Group 2 received CYD vaccination whereas the subjects from Group 1 received no vaccination. Analysis was performed on safety analysis set (SafAS) which included subjects who had received at least one dose of the study vaccines. Here, 'n'=subjects with available data for

each specified categories and '99999' signifies that the subjects from Group 1 did not receive any vaccination at Visit 2 and Visit 5 and therefore were not evaluable.

End point type	Secondary

End point timeframe:

Within 30 minutes after any and each vaccination

End point values	CYD Dengue Vaccine + Gardasil (Concomitant Administration)	CYD Dengue Vaccine + Gardasil (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	260		
Units: subjects				
number (not applicable)				
Post any vaccination (n=263,260)	0	3		
Post vaccination 1 (Visit 1) (n=263,260)	0	1		
Post CYD vaccination 1 (Visit 2) (n=0,256)	99999	1		
Post vaccination 2 (Visit 4) (n=257,256)	0	0		
Post CYD vaccination 2 (Visit 5) (n=0,249)	99999	1		
Post CYD vaccination 3 (Visit 7) (n=103, 83)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Solicited Injection Site Reactions Following Vaccination With Gardasil or CYD Dengue Vaccine

End point title	Number of Subjects Reporting Solicited Injection Site Reactions Following Vaccination With Gardasil or CYD Dengue Vaccine

End point description:

A solicited reaction (SR) was an adverse reaction (AR) observed and reported under the conditions (symptom and onset) prelisted (i.e., solicited) in the CRF and considered as related to vaccination. Solicited injection site reactions included pain, erythema, and swelling. Analysis was performed on SafAS. Here, 'n'=subjects with available data for each specified categories.

End point type	Secondary

End point timeframe:

Up to 7 days after any and each vaccination

End point values	CYD Dengue Vaccine + Gardasil (Concomitant Administration)	CYD Dengue Vaccine + Gardasil (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	260		
Units: subjects				
number (not applicable)				
Pain: Post any CYD/Gardasil vaccine (n=260,258)	206	193		
Pain: Post CYD/Gardasil vaccination 1 (n=260,258)	163	157		
Pain: Post CYD/Gardasil vaccination 2 (n=256,254)	151	141		
Pain: Post CYD vaccination 3 (n=103,83)	33	24		
Erythema: Post any CYD/Gardasil vaccine(n=260,258)	45	38		
Erythema:Post CYD/Gardasil vaccination1(n=260,258)	30	29		
Erythema:Post CYD/Gardasil vaccination2(n=256,254)	25	19		
Erythema:Post CYD vaccination 3 (n=103,83)	9	2		
Swelling:Post any CYD/Gardasil vaccine (n=260,258)	43	31		
Swelling:Post CYD/Gardasil vaccination1(n=260,258)	22	22		
Swelling:Post CYD/Gardasil vaccination2(n=256,254)	30	18		
Swelling:Post CYD vaccination 3 (n=103,83)	9	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Solicited Systemic Reactions Following Vaccination With Gardasil or CYD Dengue Vaccine

End point title	Number of Subjects Reporting Solicited Systemic Reactions Following Vaccination With Gardasil or CYD Dengue Vaccine

End point description:

A SR was an AR observed and reported under the conditions (symptom and onset) prelisted (i.e., solicited) in the CRF and considered as related to vaccination. Solicited systemic reactions included fever, headache, malaise, myalgia, and asthenia. At Visit 1 and Visit 4, subjects from Group 1 received both Gardasil and CYD vaccination and subjects from Group 2 received only Gardasil vaccination. At Visit 2 and Visit 5, only subjects from Group 2 received CYD vaccination whereas the subjects from Group 1 received no vaccination. Analysis was performed on SafAS. Here, 'n'=subjects with available data for each specified categories. Here '99999' signifies that the subjects from Group 1 did not receive any vaccination at Visit 2 and Visit 5 and therefore were not evaluable.

End point type	Secondary

End point timeframe:

Up to 14 days after any and each vaccination

End point values	CYD Dengue Vaccine + Gardasil (Concomitant Administration)	CYD Dengue Vaccine + Gardasil (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	260		
Units: subjects				
number (not applicable)				
Fever: Post any vaccination (n=259,258)	36	47		
Fever: Post vaccination 1 (Visit 1) (n=257,258)	21	8		
Fever: Post CYD vaccination 1 (Visit 2) (n=0,255)	99999	15		
Fever: Post vaccination 2 (Visit 4) (n=252,253)	10	11		
Fever: Post CYD vaccination 2 (Visit 5) (n=0,249)	99999	12		
Fever: Post CYD vaccination 3 (Visit 7) (n=103,83)	8	6		
Headache: Post any vaccination (n=260,258)	125	146		
Headache: Post vaccination 1 (Visit 1)(n=260,258)	99	93		
Headache: Post CYD vaccination 1(Visit 2)(n=0,255)	99999	73		
Headache: Post vaccination 2 (Visit 4)(n=256,254)	61	70		
Headache: Post CYD vaccination 2(Visit 5)(n=0,249)	99999	51		
Headache:Post CYD vaccination 3(Visit 7)(n=103,83)	15	17		
Malaise: Post any vaccination(n=260,258)	111	137		
Malaise: Post vaccination 1 (Visit 1)(n=260,258)	82	78		
Malaise: Post CYD vaccination 1 (Visit 2)(n=0,255)	99999	69		
Malaise: Post vaccination 2 (Visit 4)(n=256,254)	57	54		
Malaise:Post CYD vaccination 2 (Visit 5)(n=0,249)	99999	40		
Malaise:Post CYD vaccination 3 (Visit 7)(n=103,83)	20	17		
Myalgia: Post any vaccination (n=260,258)	127	156		
Myalgia: Post vaccination 1 (Visit 1) (n=260,258)	93	94		
Myalgia: Post CYD vaccination 1 (Visit 2)(n=0,255)	99999	63		
Myalgia: Post vaccination 2 (Visit 4) (n=256,254)	72	70		
Myalgia: Post CYD vaccination 2 (Visit 5)(n=0,249)	99999	43		
Myalgia:Post CYD vaccination 3 (Visit 7)(n=103,83)	16	13		

Asthenia: Post any vaccination(n=260,258)	133	132		
Asthenia: Post vaccination 1 (Visit 1) (n=260,258)	101	89		
Asthenia:Post CYD vaccination 1 (Visit 2)(n=0,255)	99999	63		
Asthenia: Post vaccination 2 (Visit 4)(n=256,254)	74	46		
Asthenia:Post CYD vaccination 2 (Visit 5)(n=0,249)	99999	35		
Asthenia:Post CYD vaccination 3(Visit 7)(n=103,83)	19	16		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Unsolicited Adverse Events Following Vaccination With Gardasil or CYD Dengue Vaccine

End point title	Number of Subjects Reporting Unsolicited Adverse Events Following Vaccination With Gardasil or CYD Dengue Vaccine

End point description:

An unsolicited AE was an observed AE that did not fulfill the conditions prelisted in the CRF in terms of diagnosis and/or onset post-vaccination. At Visit 1 and Visit 4, subjects from Group 1 received both Gardasil and CYD vaccination and subjects from Group 2 received only Gardasil vaccination. At Visit 2 and Visit 5, only subjects from Group 2 received CYD vaccination whereas the subjects from Group 1 received no vaccination. Analysis was performed on SafAS. Here, 'n'=subjects with available data for each specified categories and '99999' signifies that the subjects from Group 1 did not receive any vaccination at Visit 2 and Visit 5 and therefore were not evaluable.

End point type	Secondary

End point timeframe:

Up to 28 days after any and each vaccination

End point values	CYD Dengue Vaccine + Gardasil (Concomitant Administration)	CYD Dengue Vaccine + Gardasil (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	260		
Units: subjects				
number (not applicable)				
Post any vaccination (n=263, 260)	54	91		
Post vaccination 1 (Visit 1) (n=263, 260)	34	38		
Post CYD vaccination 1 (Visit 2) (n=0,256)	99999	38		
Post vaccination 2 (Visit 4) (n=257,256)	24	22		
Post CYD vaccination 2 (Visit 5) (n=0,249)	99999	28		
Post CYD vaccination 3 (Visit 7) (n=103,83)	5	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Non-serious Adverse Event of Special Interests (AESIs) Following Vaccination With Gardasil or CYD Dengue Vaccine

End point title	Number of Subjects Reporting Non-serious Adverse Event of Special Interests (AESIs) Following Vaccination With Gardasil or CYD Dengue Vaccine

End point description:

AESI were AEs that were considered by the Sponsor to be relevant for the monitoring of the safety profile of the investigational vaccine. At Visit 1 and Visit 4, subjects from Group 1 received both Gardasil and CYD vaccination and subjects from Group 2 received only Gardasil vaccination. At Visit 2 and Visit 5, only subjects from Group 2 received CYD vaccination whereas the subjects from Group 1 received no vaccination. Analysis was performed on SafAS. Here, 'n'=subjects with available data for each specified categories and '99999' signifies that the subjects from Group 1 did not receive any vaccination at Visit 2 and Visit 5 and therefore were not evaluable.

End point type	Secondary

End point timeframe:

Within 7 days after any and each vaccination

End point values	CYD Dengue Vaccine + Gardasil (Concomitant Administration)	CYD Dengue Vaccine + Gardasil (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	260		
Units: subjects				
number (not applicable)				
Post any vaccination (n=263,260)	0	0		
Post vaccination 1 (Visit 1) (n=263,260)	0	0		
Post CYD vaccination 1 (Visit 2) (n=0,256)	99999	0		
Post vaccination 2 (Visit 4) (n=257,256)	0	0		
Post CYD vaccination 2 (Visit 5) (n=0,249)	99999	0		
Post CYD vaccination 3 (Visit 7) (n=103,83)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Serious Adverse Events (SAEs) Including Serious Adverse Event of Special Interests Following Vaccination With Gardasil or CYD Dengue Vaccine

End point title	Number of Subjects Reporting Serious Adverse Events (SAEs) Including Serious Adverse Event of Special Interests Following Vaccination With Gardasil or CYD Dengue Vaccine

End point description:

SAEs were AEs that resulted in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalisation; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly or a medically important event. An AESIs were AEs that were considered by the Sponsor to be relevant for the monitoring of the safety profile of the investigational vaccine. Analysis was performed on SafAS.

End point type	Secondary

End point timeframe:

From Day 0 up to 6 months after the last Gardasil or CYD vaccination

End point values	CYD Dengue Vaccine + Gardasil (Concomitant Administration)	CYD Dengue Vaccine + Gardasil (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	260		
Units: subjects				
number (not applicable)				
SAE	11	8		
Serious AESI	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Cases of Virologically Confirmed Dengue (VCD) Hospitalisation Following Vaccination With Gardasil or CYD Dengue Vaccine

End point title	Number of Subjects Reporting Cases of Virologically Confirmed Dengue (VCD) Hospitalisation Following Vaccination With Gardasil or CYD Dengue Vaccine

End point description:

Hospitalised suspected dengue case was defined as an acute febrile illness with diagnosis of dengue requiring hospitalisation (with bed attribution). In such cases, 1 unplanned acute blood sample (within the first 5 days after fever onset) was collected for virological confirmation of hospitalised suspected dengue case. A suspected case was considered VCD if there was a detection of wild type dengue virus by dengue non-structural protein 1 antigen enzyme-linked immunosorbent assay and/or dengue reverse transcriptase-polymerase chain reactions. Analysis was performed on SafAS.

End point type	Secondary

End point timeframe:

From Day 0 up to 6 months after the last Gardasil or CYD vaccination

End point values	CYD Dengue Vaccine + Gardasil (Concomitant Administration)	CYD Dengue Vaccine + Gardasil (Sequential Administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	260		
Units: subjects				
number (not applicable)	1	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The AE data were collected from Day 0 up to Day 28 post any vaccination. SR were collected from Day 0 up to Day 14 post any vaccination. The SAEs were collected throughout the trial, i.e. 6 months after last Gardasil or CYD vaccination.

Adverse event reporting additional description:

SR was an AE that was prelisted (i.e.,solicited) in the electronic CRF and considered to be related to vaccination (adverse drug reaction). An unsolicited AE was an observed AE that did not fulfill the conditions prelisted in the CRF (i.e.,solicited) in terms of diagnosis and/or onset post-vaccination. Analysis was performed on SafAS.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	CYD Dengue Vaccine + Gardasil (Concomitant Administration)

Reporting group description:

Dengue immune subjects received 3 doses of CYD dengue vaccine 0.5 mL SC at Day 0, Month 6, and Month 12; whereas dengue non-immune subjects received only 2 doses of CYD vaccine at Day 0 and Month 6. Both immune and non-immune subjects received 2 doses of Gardasil vaccine 0.5 mL IM, concomitantly with the first 2 doses of CYD dengue vaccine.

Reporting group title	CYD Dengue Vaccine + Gardasil (Sequential Administration)

Reporting group description:

Dengue immune subjects received 3 doses of CYD dengue vaccine 0.5 mL SC at Month 1, Month 7, and Month 13; whereas dengue non-immune subjects received only 2 doses of CYD vaccine at Month 1 and Month 7. Both immune and non-immune subjects received 2 doses of Gardasil vaccine 0.5 mL IM at Day 0 and Month 6 sequentially (i.e., one month before) to each of the first 2 doses of CYD dengue vaccine.

Serious adverse events	CYD Dengue Vaccine + Gardasil (Concomitant Administration)	CYD Dengue Vaccine + Gardasil (Sequential Administration)	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 263 (4.18%)	8 / 260 (3.08%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 263 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sports Injury			

subjects affected / exposed	0 / 263 (0.00%)	2 / 260 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon Rupture			
subjects affected / exposed	1 / 263 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 263 (0.76%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillar Hypertrophy			
subjects affected / exposed	0 / 263 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Glomerulonephritis Acute			
subjects affected / exposed	1 / 263 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 263 (0.38%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chikungunya Virus Infection			
subjects affected / exposed	1 / 263 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue Fever			
subjects affected / exposed	1 / 263 (0.38%)	2 / 260 (0.77%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastroenteritis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingival Abscess			
subjects affected / exposed	0 / 263 (0.00%)	1 / 260 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 263 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Mycoplasmal			
subjects affected / exposed	1 / 263 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral Infection			
subjects affected / exposed	1 / 263 (0.38%)	0 / 260 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	CYD Dengue Vaccine + Gardasil (Concomitant Administration)	CYD Dengue Vaccine + Gardasil (Sequential Administration)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	233 / 263 (88.59%)	235 / 260 (90.38%)	
Nervous system disorders			
Headache	Additional description: Headache events that occurred after 14 days post-vaccination were considered as unsolicited AE.		

subjects affected / exposed	126 / 263 (47.91%)	147 / 260 (56.54%)	
occurrences (all)	178	311	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	133 / 263 (50.57%)	132 / 260 (50.77%)	
occurrences (all)	194	249	
Injection Site Erythema			
subjects affected / exposed	45 / 263 (17.11%)	38 / 260 (14.62%)	
occurrences (all)	99	63	
Injection Site Pain			
subjects affected / exposed	206 / 263 (78.33%)	193 / 260 (74.23%)	
occurrences (all)	532	452	
Injection Site Swelling			
subjects affected / exposed	43 / 263 (16.35%)	31 / 260 (11.92%)	
occurrences (all)	89	48	
Malaise			
subjects affected / exposed	111 / 263 (42.21%)	137 / 260 (52.69%)	
occurrences (all)	159	260	
Pyrexia	Additional description: Pyrexia events that occurred after 14 days post-vaccination were considered as unsolicited AE.		
subjects affected / exposed	39 / 263 (14.83%)	53 / 260 (20.38%)	
occurrences (all)	43	61	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	127 / 263 (48.29%)	156 / 260 (60.00%)	
occurrences (all)	181	283	
Infections and infestations			
Upper Respiratory Tract Infection			
subjects affected / exposed	20 / 263 (7.60%)	30 / 260 (11.54%)	
occurrences (all)	21	37	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 January 2018	Amendment was prepared following the recommendations from IDMC and the conduct of exploratory analyses, issued in November 2017, showed that the efficacy and safety profile of the CYD dengue vaccine was different between dengue immune (seropositive) and dengue non-immune (seronegative) prior to dengue vaccination. Following changes were made as per Protocol Amendment, only subjects identified as dengue immune (seropositive) at Baseline and who consented to receive the remaining injection of dengue vaccine were to continue vaccination in the study (i.e., 1 additional dose of CYD dengue vaccine). Subjects identified as dengue non-immune (seronegative) at baseline were not to receive further injections of CYD dengue vaccine but were to be able to continue in the study for a 6-month safety follow-up. They were to be proposed to have a blood sample for the assessment of HPV antibodies after the 2 doses of Gardasil vaccine if they returned into the study for Month 7.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Change of population for non-inferiority reduced to dengue immune subjects and time window for 3rd vaccination not reached (study hold), hence non-inferiority analysis not performed and immunogenicity was performed on FAS and not on Per Protocol Set.

Notes: